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     (FILE 'HCAPLUS' ENTERED AT 14:02:48 ON 10 MAR 2005)
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     FILE 'REGISTRY' ENTERED AT 14:04:53 ON 10 MAR 2005
               E INSULIN/CN
L1             1 S E3
L2            27 S 9004-10-8/CRN
L3             1 S 25322-68-3
L4          9945 S 25322-68-3/CRN
L5             0 S L2 AND L4

     FILE 'HCAPLUS' ENTERED AT 14:06:17 ON 10 MAR 2005
L6          1862 S L1/D
L7         22045 S L3/D
L8        136296 S INSULIN OR L6
L9        100468 S L7 OR POLYETHYLENE GLYCOL OR PEG OR POLYOXYETHYLENE?
L10          234 S L8 (L) L9
L11        86284 S CONJUGATE#
L12           47 S L11 (L) L10
L13           20 S L8 (L) OLIGOMER (L) L11
               SET SFIELD BI
L14           61 S L12 OR L13
L15       232414 S ORAL?
L16           14 S L15 AND L14
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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 14:11:53 ON 10 MAR 2005
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FILE COVERS 1907 - 10 Mar 2005  VOL 142 ISS 11
FILE LAST UPDATED: 9 Mar 2005  (20050309/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d que l16
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN/CN
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  25322-68-3
L6          1862 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1/D
L7         22045 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3/D
L8        136296 SEA FILE=HCAPLUS ABB=ON  PLU=ON  INSULIN/OBI OR L6
L9        100468 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 OR POLYETHYLENE GLYCOL/OBI
                 OR PEG/OBI OR POLYOXYETHYLENE?/OBI
L10          234 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (L) L9
L11        86284 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CONJUGATE#/OBI
L12           47 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 (L) L10
L13           20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (L) OLIGOMER/OBI (L) L11
L14           61 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 OR L13
L15       232414 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ORAL?
L16           14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND L14


=> d .ca l16 1-14

L16  ANSWER 1 OF 14  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:489100  HCAPLUS
DOCUMENT NUMBER:          142:204368
TITLE:                    Development and in vivo evaluation of an oral
                          insulin-PEG delivery system
AUTHOR(S):                Calceti, P.; Salmaso, S.; Walker, G.;
                          Bernkop-Schnurch, A.
CORPORATE SOURCE:         Department of Pharmaceutical Sciences, University of
                          Padua, Padua, 35131, Italy
SOURCE:                   European Journal of Pharmaceutical Sciences (2004),
                          22(4), 315-323
                          CODEN: EPSCED; ISSN: 0928-0987
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
ED   Entered STN:  17 Jun 2004
```

AB Insulin-monomethoxypoly(ethylene glycol) derivs. were obtained by preparation of mono- and di-terbutyl carbonate insulin derivs., reaction of available protein amino groups with activated 750 Da PEG and, finally, amino group de-protection. This procedure allowed for obtaining high yield of insulin-1PEG and insulin-2PEG. In vivo studies carried out by s.c. injection into diabetic mice demonstrated that the two bioconjugates maintained the native biol. activity. In vitro, PEGylation was found to enhance the hormone stability towards proteases. After 1 h incubation with elastase, native insulin, insulin-1PEG and insulin-2PEG undergo about 70, 30 and 10% degradation, resp., while in the presence of pepsin protein degradation was 100, 70 and 50%, resp. The attachment of low mol. weight PEG did not significantly (P>0.05) alter insulin permeation behavior across the intestinal mucosa. Insulin-1PEG was formulated into mucoadhesive tablets constituted by the thiolated polymer poly(acrylic acid)-cysteine. The therapeutic agent was sustained released from these tablets within 5 h. In vivo, by **oral** administration to diabetic mice, the glucose levels were found to decrease of about 40% since the third hour from administration and the biol. activity was maintained up to 30 h. According to these results, the combination of PEGylated insulin with a thiolated polymer used as drug carrier matrix might be a promising strategy for **oral** insulin administration.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 34, 35

ST **insulin PEG conjugate** tablet **oral**
thiolated polymer

IT Biological transport
(permeation; synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT Antidiabetic agents
Diabetes mellitus
Dissolution
Drug delivery systems
Protein degradation
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT Polyoxyalkylenes, preparation
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT Drug delivery systems
(tablets, mucoadhesive; synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 11070-73-8, Bovine **Insulin**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugated** to **PEG**; synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 9004-74-4, Monomethoxypoly(ethylene glycol)
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugates** with **insulin**; synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 70-18-8, Glutathione, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 124661-64-9DP, **conjugates** with **insulin**

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 11070-73-8DP, Bovine **Insulin**, reaction with t-butyloxycarbonyl and **PEG** derivs. **25322-68-3DP**, **PEG**, reaction with bovine **insulin**
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 124661-64-9P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

IT 52-90-4D, L-Cysteine, reaction products with poly(acrylic acid)
9003-01-4D, Poly(acrylic acid), reaction products with L-cysteine
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and activity of **insulin-PEG conjugate** delivered in tablet form)

L16 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:392077 HCAPLUS
DOCUMENT NUMBER: 140:412315
TITLE: **Oral** compositions containing active ingredient coated on particles of cellulose or calcium phosphate
INVENTOR(S): Ruff, Michael D.; Cobb, Joseph E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 38 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004091544	A1	20040513	US 2003-643319	20030819
WO 2004043356	A2	20040527	WO 2003-US35075	20031104
WO 2004043356	A3	20041104		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 2002-425024P	P	20021108
US 2003-643319	A	20030819

ED Entered STN: 14 May 2004
AB Disclosure is an **oral** formulation containing an active pharmaceutical ingredient, for instance a peptide pharmaceutical, such as insulin, coated onto a suitable particulate substrate, which is not a polysaccharide, such as a cellulose or a calcium phosphate. The **oral** formulation may be a modified release formulation, for

instance a controlled release formulation or a sustained release formulation, or may be an immediate release formulation. Also, the formulation may be encapsulated in gelatin capsules or may be compressed into tablets. The thus obtained dosage forms are especially suitable for delivery of drugs that are incompatible with sugars, such as insulin, due to their polysaccharide-free nature. For example, sustained release gelatin capsules containing polydispersed hexyl insulin monoconjugate 5.8, Emcompress (dicalcium phosphate dihydrate) 209.0, capric acid 22.9, citric acid 46.6, lauric acid 46.6, Opadry YS-1-7006 18.3, sodium cholate 138.4, sodium hydroxide 54.2, sodium phosphate heptahydrate 46.4 and Surelease (Et cellulose) 210.7g was found to have a satisfied performance of insulin delivery as shown by the controlled blood glucose level.

IC ICM A61K009-16
ICS A61K038-00; B01J013-00; A61K009-50

NCL 424490000; 514002000; 427002140

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST drug coated calcium phosphate cellulose particulate **oral** delivery; insulin coated dicalcium phosphate cellulose particle sustained release capsule

IT Drug delivery systems
(capsules, sustained-release; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT Antidiabetic agents
Permeation enhancers
(coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated **oral** compns. containing peptides coated on particles of calcium phosphate and cellulose)

IT Drug delivery systems
(tablets, enteric-coated; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT Drug delivery systems
(tablets, immediate release; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT Drug delivery systems
(tablets; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT 77-90-7, Acetyl tributyl citrate 77-93-0, Triethyl citrate 471-34-1, Calcium carbonate, biological studies 557-04-0, Magnesium stearate 1592-23-0, Calcium stearate 7693-13-2, Calcium citrate 7757-93-9, Dibasic calcium phosphate 7758-23-8, Monobasic calcium phosphate 7758-87-4, Tribasic calcium phosphate 7778-18-9, Calcium sulfate 7789-77-7, EMCOMPRESS 9004-34-6, Cellets, biological studies 9004-57-3, Surelease 25212-88-8, Eudragit L30D55 25322-68-3, PEG 33434-24-1, Eudragit RS30D 117698-04-1, OPADRY YS-1-7006
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

IT 9004-10-8, Insulin, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated **oral** compns. containing insulin coated on particles of

calcium phosphate and cellulose)
IT 7631-86-9, CAB-O-SIL, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colloidal; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)
IT 9063-38-1, Sodium starch glycolate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dispersant; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)
IT 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(permeation enhancer; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)
IT **9004-10-8D, Insulin, oligomer conjugate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polydisperse; coated **oral** compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

L16 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:162445 HCAPLUS
DOCUMENT NUMBER: 140:193075
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates** and methods of treating diseases therewith
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingam; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 235,284.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038866	A1	20040226	US 2003-382155	20030305
US 2003069170	A1	20030410	US 2002-235284	20020905
US 6770625	B2	20040803		

PRIORITY APPLN. INFO.:

US 2001-318193P	P	20010907
US 2002-377865P	P	20020503
US 2002-235281	A2	20020905
US 2002-235284	A2	20020905

OTHER SOURCE(S): MARPAT 140:193075
ED Entered STN: 29 Feb 2004
AB Pharmaceutical compns. that include insulin, an insulin drug-oligomer conjugate, a fatty acid component, and a bile salt component or a bile salt component without a fatty acid component are described. The insulin drug is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component, when together, can be present in a weight-to-weight ratio of between 1:15 and 15:1. Methods of treating an insulin deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. Substantial redns. in blood glucose were observed as

the result of coadministration of hexyl-insulin monoconjugate 2 (HIM2) and bile salts to mice and dogs. All of the bile salts were effective at a level of 1.5 %.

IC ICM A61K038-28
ICS A61K031-57

NCL 514003000; 514171000

CC 1-10 (Pharmacology)
Section cross-reference(s): 63

ST pharmaceutical **insulin** drug **oligomer conjugate**
antidiabetic; blood glucose redn **insulin conjugate**
bile salt

IT Fatty acids, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C4-20; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(buccal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Alkanes, biological studies
Oligomers
Polyoxyalkylenes, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with **insulin**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Digestive tract
(**insulin oligomer conjugate** delivery across wall of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(liqs., **oral**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(liqs.; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(nasal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Antidiabetic agents
Drug delivery systems
(**oral**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(parenterals; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Antidiabetic agents
Buffers
Drug delivery systems
Human
Hydrophilicity
Lipophilicity
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Bile salts
Fatty acids, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer**

conjugates for treating diseases)
IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)
IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Flavoring materials
(strawberry; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(tablets; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(transdermal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficiency or disorder, treatment of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)
IT 81-24-3 81-25-4 83-44-3 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 145-42-6, Sodium taurocholate 334-48-5, Capric acid 360-65-6 361-09-1, Sodium Cholate 516-50-7 863-57-0 1180-95-6, Sodium taurodeoxycholate 2898-95-5, Sodium ursodeoxycholate **9004-10-8D**, **Insulin**, **conjugates** with **oligomers** 11061-68-0D, **Insulin** (human), **conjugates** with methoxy(**polyethylene glycol**) hexanoic acid 11061-68-0D, **Insulin** (human), **conjugates** with polypropylenglycols **25322-68-3D**, **Polyethylene glycol**, **conjugates** with **insulin** 116094-23-6D, AspB28insulin, human, **conjugates** with **oligomers** 133107-64-9D, **conjugates** with **oligomers** 326892-09-5D, **conjugates** with human **insulin** 452310-88-2D, **conjugates** with **oligomers** 452310-92-8D, **conjugates** with **oligomers** 452311-02-3D, **conjugates** with **oligomers** 452311-09-0D, **conjugates** with **oligomers** 452311-17-0D, **conjugates** with **oligomers** 452311-24-9D, **conjugates** with **oligomers** 452311-26-1D, **conjugates** with **oligomers** 452311-27-2D, **conjugates** with **oligomers** 452311-29-4D, **conjugates** with **oligomers** 452311-30-7D, **conjugates** with **oligomers** 452311-31-8D, **conjugates** with **oligomers** 452311-32-9D, **conjugates** with **oligomers** 452311-33-0D, **conjugates** with **oligomers** 452311-35-2D, **conjugates** with **oligomers** 452311-36-3D, **conjugates** with **oligomers** 452311-37-4D, **conjugates** with **oligomers** 502487-21-0D, **conjugates** with human **insulin** 502495-36-5D, **conjugates** with **oligomers** 663602-55-9D, **conjugates** with human

insulin 663602-56-0D, **conjugates** with human **insulin**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-27-6, Triethylene glycol 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 124-63-0, Methanesulfonyl chloride 141-78-6, EtOAc, reactions 623-65-4, Palmitic anhydride 865-47-4 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6, 8-Bromooctanoic acid 25322-68-3, PEG6 25952-53-8, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 3639-35-8P 4437-01-8P, Heptaethylene glycol monomethyl ether 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 29823-21-0P 70802-40-3P 74654-05-0P 86259-87-2P, Tetraethylene glycol monobenzyl ether 105292-71-5P 124668-93-5P 142556-85-2P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-73-8P 477775-74-9P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-23-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 27425-92-9P, Decaethylene glycol monomethyl ether 62304-85-2P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477788-13-9P 502487-22-1P 502487-24-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 69-65-8, Mannitol 77-86-1, Tromethamine 77-92-9, Citric Acid, biological studies 102-71-6, Trolamine, biological studies 557-04-0, Magnesium Stearate 994-36-5, Sodium Citrate 1310-73-2, Sodium Hydroxide, biological studies 7558-79-4, Dibasic Sodium Phosphate 7558-80-7, Sodium Phosphate Monobasic 7647-01-0, Hydrochloric Acid, biological studies 7732-18-5, Water, biological studies 9004-34-6, Cellulose, biological studies 9063-38-1, Explotab 56038-13-2, Sucralose 74811-65-7, Croscarmellose Sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

L16 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1006707 HCAPLUS
DOCUMENT NUMBER: 140:35957
TITLE: Methods of reducing hypoglycemic episodes in the treatment of diabetes mellitus by **orally** administering an **insulin-oligomer** **conjugate**
INVENTOR(S): Still, James Gordon; Kosutic, Gordana
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003105768	A2	20031224	WO 2003-US18763	20030613
WO 2003105768	A3	20040311		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004038867	A1	20040226	US 2003-461199	20030613
PRIORITY APPLN. INFO.:			US 2002-388988P P	20020613

OTHER SOURCE(S): MARPAT 140:35957
ED Entered STN: 26 Dec 2003
AB The present invention provides compns. and methods for reducing hypoglycemic episodes experienced by a subject in need of treatment for diabetes mellitus, said method comprising **orally** administering an amount of an insulin polypeptide-oligomer conjugate to the subject, wherein: (i) the amount of the insulin polypeptide-oligomer conjugate reduces the number and/or severity of hypoglycemic episodes experienced by the subject during a given time period when compared with the number and/or severity of hypoglycemic episodes that would have been experienced during a similar time period by the subject or by subjects in a control group parenterally administered insulin or an insulin analog in an amount that provides a substantially equivalent level of glycemic control; and (ii) the oligomer of the insulin polypeptide-oligomer conjugate comprises a hydrophilic moiety and a lipophilic moiety. Patients with type 1 diabetes were treated p.o. with HIM2 (human insulin with -C(O)(CH2)5(OC2H4)7OCH3 conjugated to the B29 lysine) in comparison with treatment with insulin lispro, s.c. Hypoglycemic events that required rescue intervention were significantly lower in the HIM2 treatment group as compared to the insulin lispro treatment group.
IC ICM A61K
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
ST **insulin conjugate** reducing hypoglycemic episode diabetes mellitus; **oral insulin oligomer conjugate** hypoglycemia redn antidiabetic; HIM2 **oral** antidiabetic redn hypoglycemic episode
IT Drug delivery systems
(capsules; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT **Oligomers**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic-lipophilic, **conjugates** with **insulin**; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT Diabetes mellitus
(**insulin**-dependent; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Drug delivery systems
(liqs., **oral**; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT Hydrophilicity
Lipophilicity
(of **oligomer**; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT Diabetes mellitus
Human
Hypoglycemia
Postprandial period
(**oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT Antidiabetic agents
(**oral**; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT Flavoring materials
(strawberry; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIM2 **conjugate** maintenance of two-hour postprandial blood levels of; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT 9035-68-1, Proinsulin
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation conjugation of; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT 9002-07-7, Trypsin 9025-24-5, Carboxypeptidase B
RL: CAT (Catalyst use); USES (Uses)
(in HIM2 **conjugate** preparation from proinsulin; **oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT 223714-27-0P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT **9004-10-8D**, **Insulin**, **conjugates** with hydrophilic-lipophilic **oligomer** 502487-21-0D, **conjugates** with **insulin**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**oral insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)
IT 57-55-6, Propylene glycol, biological studies 77-86-1, Tris(hydroxymethyl)aminomethane 77-92-9, Citric acid, biological studies 102-71-6, Triethanolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 1310-73-2, Sodium hydroxide, biological studies 7632-05-5, Sodium phosphate 7732-18-5, Water, biological studies 56038-13-2, Sucralose
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**oral insulin-oligomer conjugate**
for reducing hypoglycemic episodes in treatment of diabetes mellitus)

L16 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:221462 HCAPLUS
DOCUMENT NUMBER: 138:260437
TITLE: Pharmaceutical compositions of drug-oligomer conjugates for **oral** administration
INVENTOR(S): Soltero, Richard; Ekwuribe, Nnochiri N.; Opawale, Foyeke; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022210	A2	20030320	WO 2002-US28536	20020906
WO 2003022210	A3	20031218		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003083232	A1	20030501	US 2002-235381	20020905
PRIORITY APPLN. INFO.:			US 2001-318193P P	20010907
			US 2002-377865P P	20020503

ED Entered STN: 21 Mar 2003
AB An **oral** pharmaceutical composition comprising a drug-oligomer conjugate, 0.1-15% of a fatty acid component, and 0.1-15% of a bile salt component is described. The drug, e.g., a peptide or protein, is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating diseases in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. For example, tablets containing an insulin conjugate HIM2 were prepared by lyophilization of a mixture containing HIM2 2.5 g, Na cholate 30.0 g, oleic acid 10.0 g, 25% sucralose 8.0 g, flavor 4.0 g, capric acid 5.0 g, lauric acid 5.0 g, citric acid 67.2 g, trolamine 42.4 g, NaOH 18.8 g, pH adjusters (5N NaOH and 5N HCl) as needed, and water resulting in an amorphous powder. The powder (127.6 g) was blended with citric acid 29.7 g, sodium citrate 84.2 g, Tris base 106.7 g, microcryst. cellulose 24.8 g, and Explotab 9.4 g and compressed into tablets.
IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 35
ST **oral** drug oligomer conjugate bile salt fatty acid; peptide protein drug oligomer conjugate **oral**
IT Drug delivery systems

(liqs., **oral**; **oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-chain; **oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medium-chain; **oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Antidiabetic agents
Buffers
Human
(**oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Bile salts
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Drug delivery systems
(**oral**; **oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT Drug delivery systems
(tablets; **oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT 11061-68-0D, Human **insulin**, **conjugates** with methoxy(**polyethylene glycol**) hexanoic acid 326892-09-5D, **conjugates** with human **insulin**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**oral** compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

IT 9007-12-9D, Calcitonin, oligomer conjugates 59112-80-0D, C-Peptide, oligomer conjugates
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT 77-86-1, Tromethamine 102-71-6, Trolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 47931-85-1D, Salmon calcitonin, oligomer conjugates 477775-65-8D, drug conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**oral** compns. of drug-oligomer conjugates containing bile salt and fatty acid)

IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6, 8-Bromooctanoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of oligomers for drug-oligomer conjugates for **oral** delivery)

IT 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 10108-28-8P 24342-68-5P 27425-92-9P 29823-21-0P 60037-74-3P 74654-05-0P 86259-87-2P 113395-48-5P 124668-93-5P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P

477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P
477788-13-9P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P
502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of oligomers for drug-oligomer conjugates for **oral** delivery)

L16 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:221460 HCAPLUS
DOCUMENT NUMBER: 138:260435
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates**
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingham; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003022208	A2	20030320	WO 2002-US28429		20020906
WO 2003022208	A3	20030925			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003083232	A1	20030501	US 2002-235381		20020905
PRIORITY APPLN. INFO.:			US 2001-318193P	P	20010907
			US 2002-377865P	P	20020503

OTHER SOURCE(S): MARPAT 138:260435
ED Entered STN: 21 Mar 2003
AB Pharmaceutical compns. that include an insulin drug-oligomer conjugate, a fatty acid component, and a bile salt component are described. The insulin drug is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating an insulin deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. E.g., PEG derivs. of fatty acids such as hexanoic acid were prepared, activated and conjugated to insulin derivs.
IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34, 35
ST **insulin PEG** fatty acid **conjugate** pharmaceutical
IT Drug delivery systems
(**oral**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT 361-09-1, Sodium cholate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT 111-77-3 112-35-6 112-60-7 112-76-5, Stearoyl chloride 623-65-4, Palmitic anhydride 2615-15-8 15848-88-1 23601-40-3, 2,5,8,11,14,17-Hexaoxanonadecan-19-ol 142556-85-2 477788-13-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT 3639-35-8P, Decanoic acid, 10-hydroxy-, ethyl ester 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 5299-60-5P, Ethyl 6-hydroxyhexanoate 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 29823-21-0P, Ethyl 8-bromooctanoate 60037-74-3P 74654-05-0P 86259-87-2P 105292-71-5P 113395-48-5P 124668-93-5P 259228-98-3P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P 477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P 502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT **9004-10-8DP**, **Insulin**, **conjugates** with fatty acid-**PEG** derivs.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT 502495-05-8 502495-19-4 502495-22-9 502495-24-1 502495-25-2 502495-35-4 502495-36-5 502495-38-7 502495-39-8 502495-40-1 502495-41-2 502495-42-3 502495-43-4 502495-44-5 502495-47-8 502495-48-9 502495-51-4 502495-52-5 502495-53-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

L16 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:184235 HCAPLUS
TITLE: Effects of amphiphilic **oligomers** on **oral insulin conjugates.** Part 3: Solubility and protease stability
AUTHOR(S): James, Kenneth D.; Willie, Kirsten; Malkar, Navdeep B.; Severynse-Stevens, Diana; Ekwuribe, Nnochiri N.
CORPORATE SOURCE: Innovation and Drug Discovery, Nobex Corporation, Durham, NC, 27713, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-269. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
ED Entered STN: 11 Mar 2003

AB The conjugation of polymers (such as polyethylene glycol; PEG) to peptide therapeutics has been known to increase the aqueous solubility and the circulation time of the parent peptide. Although the resultant peptide conjugate may have an improved pharmacodynamic profile, the large oligomers that are commonly used preclude **oral** delivery of the therapeutic. Nobex Corporation has proprietary amphiphilic oligomers (polyoxyethylene alkyl ethers) that have been applied to several peptide therapeutics to enhance their PK/PD profile and enable **oral** delivery. We now present a study of the SAR and physicochem. properties of a series of insulin conjugates in which the oligomers vary in size, sterics, and amphiphilic balance. In Part 3 of this study, we assess the effects of various oligomers on solubility at varying pH and salt concns. We also evaluate stability of the resultant conjugates to the digestive enzymes trypsin, chymotrypsin, and pepsin.

L16 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:184234 HCAPLUS
TITLE: Effects of amphiphilic **oligomers** on **oral insulin conjugates.** Part 2: Conformational changes of **conjugates**
AUTHOR(S): Malkar, Navdeep; Juska, Darius; Fields, Gregg B.; Ekwuribe, Nnochiri N.; James, Kenneth D.
CORPORATE SOURCE: Nobex Corporation, Research Triangle Park, NC, 27709, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-268. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
ED Entered STN: 11 Mar 2003
AB Amphipathic α-helixes are ubiquitous structural features observed in biol. active peptides. They play important roles in the folding, protein-protein recognition, and protein-membrane interaction of peptides. The conjugation of amphiphilic oligomers (polyoxyethylene alkyl ethers) to peptide therapeutics has been known to alter the biol. activity of the parent peptide. This may be due to alterations in the protein folding or to conformational changes in the peptide. In Part 2 of our study, we report results from CD Spectroscopy (CD) and Differential Scanning Calorimetry (DSC) of different insulin conjugates. We evaluated the effect of our amphiphilic oligomers, which vary in their size, sterics, and amphiphilic balance on the conformational changes of **oral** insulin conjugates in solution by CD. The deconvolution analyses of the conjugates were also performed. The thermal denaturation (Tm) of these insulin conjugates was determined by CD and DSC.

L16 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:184233 HCAPLUS
TITLE: Effects of amphiphilic **oligomers** on **oral insulin conjugates**
AUTHOR(S): Miller, Mark A.; Malkar, Navdeep B.; Odenbaugh, Amy L.; Surguladze, David; Danek Burgess, Krisstina S.; Bednarcik, Mark J.; Dugdell, Robert E.; Yarbrough, Kevin G.; Willie, Kirsten; Ekwuribe, Nnochiri N.; James, Kenneth D.
CORPORATE SOURCE: Nobex Corporation, Research Triangle Park, NC, 27709, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New

Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-267. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
ED Entered STN: 11 Mar 2003
AB In an effort to understand the effects of conjugating amphiphilic oligomers to insulin, a broad range of oligomers, varying in their amphiphilicity, length, and structure, were synthesized and conjugated to insulin. The physicochem. properties of the insulin conjugates, including in vitro and in vivo activity, were examined Part 1 of our study describes the synthesis of the oligomers and the activity results of the insulin conjugates. The in vitro assays measure agonist activity at the insulin receptor and the in vivo efficacy was assayed by **oral** dosing in mice. Our goal with this research is to establish a guide to generally predict the effects of amphiphilic oligomers not only on insulin, but on other proteins and peptides, thus facilitating the **oral** delivery of protein and peptide conjugates.

L16 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:657913 HCAPLUS
DOCUMENT NUMBER: 137:196046
TITLE: Methods of treating diabetes mellitus with **orally** administered insulin oligomers
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Still, James Gordon; Filbey, Jennifer Ann
PATENT ASSIGNEE(S): Nobex Corporation, USA; Radhakrishnan, Balasingam; Ansari, Aslam M.; Odenbaugh, Amy L.
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002065985	A2	20020829	WO 2002-US4440		20020214
WO 2002065985	A3	20040219			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003050228	A1	20030313	US 2002-75097		20020213
CA 2437940	AA	20020829	CA 2002-2437940		20020214
EP 1409006	A2	20040421	EP 2002-709541		20020214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004527487	T2	20040909	JP 2002-565546		20020214
PRIORITY APPLN. INFO.:			US 2001-269198P	P	20010215
			US 2002-347713P	P	20020111
			WO 2002-US4440	W	20020214

ED Entered STN: 30 Aug 2002

AB Methods of treating diabetes mellitus using an effective amount of an **oral** insulin derivative are claimed. The structure of the insulin derivative is: insulin polypeptide-B-Lj-Gk-R-G'm-R'-G"n-T wherein: B is a bonding moiety; L is a linker moiety; G, G' and G" are individually selected spacer moieties; R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety; T is a terminating moiety; and j, k, m and n are individually 0 or 1. The structure of the insulin derivative is: insulin polypeptide-X(CH2)mY(C2H4O)nR, insulin polypeptide-X(CH2)m(OC2H4)nOR, or insulin polypeptide-NH-CO-(CH2)m(OC2H4)nOR, wherein: X and Y are ester moieties, thioester moieties, ether moieties, carbamate moieties, thiocarbamate moieties, carbonate moieties, thiocarbonate moieties, amide moieties, urea moieties or covalent bonds; m is between 1 and 24; n is between 1 and 50; and R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alc. moiety, or a fatty acid moiety. A specifically claimed derivative is insulin polypeptide-NH-CO-(CH2)5(OC2H4)7OCH3. Formulations for capsules are exemplified.

IC ICM A61K

CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63

ST diabetes mellitus treatment **oral insulin oligomer conjugate**

IT Drug delivery systems
(capsules; methods of treating diabetes mellitus with **orally** administered insulin oligomers)

IT Diabetes mellitus
(insulin-dependent; methods of treating diabetes mellitus with **orally** administered insulin oligomers)

IT Antidiabetic agents
Diabetes mellitus
Human
(methods of treating diabetes mellitus with **orally** administered insulin oligomers)

IT **9004-10-8D**, **Insulin**, oligomeric **conjugates**
452310-88-2D, oligomeric **conjugates** 452310-92-8D, oligomeric **conjugates** 452311-02-3D, oligomeric **conjugates**
452311-09-0D, oligomeric **conjugates** 452311-17-0D, oligomeric **conjugates** 452311-24-9D, oligomeric **conjugates**
452311-25-0D, oligomeric **conjugates** 452311-26-1D, oligomeric **conjugates** 452311-27-2D, oligomeric **conjugates**
452311-28-3D, oligomeric **conjugates** 452311-29-4D, oligomeric **conjugates** 452311-30-7D, oligomeric **conjugates**
452311-31-8D, oligomeric **conjugates** 452311-32-9D, oligomeric **conjugates** 452311-33-0D, oligomeric **conjugates**
452311-34-1D, oligomeric **conjugates** 452311-35-2D, oligomeric **conjugates** 452311-36-3D, oligomeric **conjugates**
452311-37-4D, oligomeric **conjugates** 452311-38-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treating diabetes mellitus with **orally** administered **insulin oligomers**)

L16 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:131193 HCAPLUS
DOCUMENT NUMBER: 134:183490
TITLE: Hydrophilic and lipophilic balanced microemulsion formulations of free-form and/or conjugation-stabilized therapeutic agents such as insulin
INVENTOR(S): Ekwuribe, Nnochiri Nkem; Ramaswamy, Muthukumar; Radhakrishnan, Balasingam; Allaudeen, Hameedsulthan S.

PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: U.S., 32 pp., Cont.-in-part of U. S. 5,681,811.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6191105	B1	20010220	US 1997-958383	19971027
US 5359030	A	19941025	US 1993-59701	19930510
US 5438040	A	19950801	US 1994-276890	19940719
US 5681811	A	19971028	US 1995-509422	19950731
US 2003229006	A1	20031211	US 2003-448524	20030530
US 2003229010	A1	20031211	US 2003-448535	20030602
PRIORITY APPLN. INFO.:			US 1993-59701	A3 19930510
			US 1994-276890	A2 19940719
			US 1995-509422	A2 19950731
			US 1997-958383	A3 19971027
			US 2000-614203	A1 20000712

ED Entered STN: 22 Feb 2001

AB A therapeutic formulation comprising a microemulsion of a therapeutic agent in free and/or conjugate coupled form, wherein the microemulsion comprises a water-in-oil (w/o) microemulsion including a lipophilic phase and a hydrophilic phase, and has a hydrophilic and lipophilic balance (HLB) value between 3 and 7 is described. The therapeutic agent is selected from the group consisting of insulin, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, non-naturally occurring opioids, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminease, adenosine deaminase, RNase, trypsin, chymotrypsin, papain, Ara-A (Arabinofuranosyladenine), acylguanosine, nordeoxyguanosine, azidothymidine, dideoxyadenosine, dideoxycytidine, dideoxyinosine, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, or I-darubicin, erythromycin, vancomycin, oleandomycin, ampicillin, quinidine and heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably **oral** or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the insulin, the linear polyalkylene glycol moiety and the lipophilic moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. The microemulsion compns. of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications. For example, a microemulsion formulation was prepared containing Capmul MCM 53.0, Centrophase 31 5.7, propylene glycol 19.9, Tween 80 1.4, hexyl insulin in NaP buffer 15 mg/mL, and NaP buffer up to 100%, resp. Also, preparation of hexyl insulin conjugates with Me (ethylene glycol)7-O-hexanoic acid was carried out.

IC ICM A61K038-38
ICS C07K014-62
NCL 514003000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2

IT Drug delivery systems
(**oral**; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 9004-95-9DP, **Polyoxyethylene** cetyl ether, **conjugates** with tri-Bu AraCMP 9004-99-3DP, **Polyethylene glycol** monostearate, **conjugates** with **insulin** 9005-66-7DP, conjugates with insulin 9005-70-3DP, conjugates with polysorbate trioleate 11070-73-8DP, Bovine insulin, conjugates **25322-68-3DP**, **Polyethylene glycol**, **conjugates** with tetrahydropyran derivative and **insulin** 88517-92-4DP, **conjugates** with **insulin** and **polyethylene glycol** 212969-35-2DP, conjugates with hexyl insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as **insulin**)

IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, esters 69-53-4, Ampicillin 69-65-8, D-Mannitol 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies 1404-90-6, Vancomycin 1984-06-1, Sodium octanoate 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine 9000-96-8, Arginase 9001-73-4, Papain 9001-99-4, RNase 9002-07-7, Trypsin 9002-60-2, ACTH, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies 9004-10-8D, Insulin, conjugates with hexanoic acid derivative, biological studies 9004-10-8D, Insulin, hexyl polymer conjugate, biological studies 9005-49-6, Heparin, biological studies 9005-65-6, Tween 80 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9015-68-3, Asparaginase 9026-93-1, Adenosine deaminase 9027-98-9 9038-70-4, Somatomedin 9054-89-1, Superoxide dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25322-68-3, **Polyethylene glycol** 30516-87-1, Azidothymidine 51110-01-1, Somatostatin 58957-92-9, I-Darubicin 60118-07-2, Endorphin 69655-05-6, Dideoxyinosine 82410-32-0 87090-08-2, Labrafil M 1944 120300-18-7, Caprol PGE 860 156259-68-6, Capmul MCM 195739-92-5, Centrophase 31
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as **insulin**)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:911065 HCAPLUS
DOCUMENT NUMBER: 134:76386
TITLE: Amphiphilic drug-oligomer conjugates with hydrolyzable lipophile components and methods for making and using the same
INVENTOR(S): Ekwuribe, Nnochiri; Ramaswamy, Muthukumar; Rajagopalan, Jayanthi
PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000078302		A1	20001228	WO 2000-US16879	20000619
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6309633		B1	20011030	US 1999-336548	19990619
CA 2377517		AA	20001228	CA 2000-2377517	20000619
BR 2000011772		A	20020402	BR 2000-11772	20000619
EP 1196157		A1	20020417	EP 2000-942956	20000619
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003502364		T2	20030121	JP 2001-504366	20000619
NZ 516109		A	20040430	NZ 2000-516109	20000619
ZA 2001010099		A	20030307	ZA 2001-10099	20011207
NO 2001006143		A	20020218	NO 2001-6143	20011217
US 2004223948		A1	20041111	US 2004-774903	20040210
PRIORITY APPLN. INFO.:				US 1999-336548 A	19990619
				WO 2000-US16879 W	20000619
				US 2002-18879 A1	20020805

ED Entered STN: 29 Dec 2000

AB The present invention relates generally to hydrolyzable drug-oligomer conjugates, pharmaceutical compns. comprising such conjugates, and to methods for making and using such conjugates and pharmaceutical compns. For example, a conjugate of insulin, PEG, and oleic acid was prepared and can be **orally** administered.

IC ICM A61K031-075
ICS A61K031-13; A61K031-16; A61K031-21; A61K031-325; A61K038-02; A61K038-28

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2

IT 50-56-6, Oxytocin, biological studies 58-82-2, Bradykinin 69-25-0, Eledoisin 1066-17-7, Colistin 1393-25-5, Secretin 1404-26-8, Polymyxin b 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1407-47-2, Angiotensin 1947-37-1, Tetragastrin 5534-95-2, Pentagastrin 8049-47-6, Pancreatin 9001-01-8, Kallikrein 9001-25-6, Blood-coagulation factor VII 9001-27-8, Factor VIII 9001-28-9, Factor IX 9002-07-7, Trypsin 9002-60-2, Adrenocorticotrophin, biological studies 9002-61-3, Human chorionic gonadotropin 9002-61-3D, Human chorionic gonadotropin, β-chain 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-67-9, LH 9002-69-1, Relaxin 9002-71-5, TSH 9002-76-0, Gastrin 9002-79-3, MSH 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9011-97-6, Cholecystokinin 9013-66-5, Glutathione peroxidase 9014-42-0, Thrombopoietin 9015-68-3, Asparaginase 9015-71-8, Corticotropin-releasing factor 9015-94-5, Renin, biological studies 9034-39-3, Somatoliberin 9034-40-6, Luliberin 9038-70-4, Somatomedin 9039-53-6, Urokinase 9054-89-1, Superoxide dismutase 9061-61-4, Nerve growth factor 9063-57-4, Taftsin 9066-59-5, Lysozyme chloride 11000-17-2, Vasopressin 11062-77-4, Superoxide 11085-36-2, Human placental lactogen 11096-26-7, Erythropoietin 11128-99-7, Angiotensin II 12038-82-3 16679-58-6, Desmopressin 17650-98-5, Caerulein 24305-27-9, TRH 25126-32-3, Cholecystokinin-8 (swine) 33507-63-0, Substance P 37221-79-7, Vasoactive intestinal peptide 37231-28-0, Melittin 39379-15-2, Neurotensin 51110-01-1D, Somatostatin, derivs. 52906-92-0, Motilin 53678-77-6, Muramyldipeptide 59392-49-3, Gastric

inhibitory peptide 60118-07-2, Endorphin 60529-76-2, Thymopoietin 61512-21-8, Thymosin 61912-98-9, **Insulin**-like growth factor 62229-50-9, Epidermal growth factor 62683-29-8, CSF 63340-72-7, Thymic humoral factor 67763-96-6, **Insulin**-like growth factor I 67763-97-7, **Insulin**-like growth factor II 70904-56-2, Kyotorphin 74913-18-1, Dynorphin 78922-62-0, Serum thymic factor 80043-53-4, Gastrin-releasing peptide 81627-83-0, MCSF 82785-45-3, Neuropeptide Y 83652-28-2, Calcitonin gene related peptide 83869-56-1, GM-CSF 85637-73-6, Atrial natriuretic peptide 103370-86-1, PTH-related protein 105250-86-0, Ebiratide 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor 106388-42-5, Peptide YY 116243-73-3, Endothelin 117148-67-1, Pancreastatin 119418-04-1, Galanin 130939-66-1, NT-3 143011-72-7, GCSF 143375-33-1, Neurotrophin 4
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

IT 112-27-6, Triethylene glycol 112-77-6, Oleoyl chloride 7693-46-1, p-Nitrophenyl chloroformate 9004-10-8, **Insulin**, reactions 25322-68-3, Peg
RL: RCT (Reactant); RACT (Reactant or reagent)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

IT 112-27-6DP, Triethylene glycol, derivs., **conjugates** with **insulin** 7535-00-4DP, Galactosamine, **conjugates** with **PEG insulin 9004-10-8DP**, **Insulin**, **conjugates** with **PEG** derivs., biological studies 9004-81-3DP, Polyethylene glycollaurate, **conjugates** with **insulin** 9004-96-0DP, **Polyethylene glycol** oleate, **conjugates** with **insulin** 10233-14-4DP, Triethylene glycol oleate, **conjugates** with **insulin** 28397-10-6DP, Octanoic acid, 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester, **conjugates** with **insulin** 62304-85-2DP, Hexadecanoic acid, 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester, **conjugates** with **insulin**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:672439 HCAPLUS
DOCUMENT NUMBER: 134:212549
TITLE: Stability and physical characteristics of **orally** active amphiphilic human insulin analog, methoxy (polyethylene glycol) hexanoyl human recombinant insulin (HIM2)
AUTHOR(S): Krishnan, B. Radha; Rajagopalan, J. S.; Burnham, J.
CORPORATE SOURCE: Protein Delivery Inc., Durham, NC, 27713, USA
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000), 27th, 1038-1039
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Sep 2000

AB **Orally** active HIM2, an amphiphilic oligomer attached to B29-Lys of human insulin, showed significant thermal stability in aqueous buffer and in solid state over unmodified insulin. The change in pi value as the result of modification at B29-Lys suggests that the dissoln. and solubility profile of HIM2 would be different from that of insulin in the gastrointestinal tract. The chemical modification contributed to a concurrent increase in hydrodynamic radius of insulin but unaltered the self-association state (monomeric) of insulin at low protein concentration
CC 63-5 (Pharmaceuticals)
ST **oral** human **insulin** analog stability property; **polyethylene glycol** human **insulin** **conjugate** stability
IT Dissolution
Self-association
(stability and phys. characteristics of **orally** active amphiphilic human insulin analog, methoxy(polyethylene glycol) hexanoyl human recombinant insulin)
IT 11061-68-0D, Human **insulin**, **conjugates** with methoxy(**polyethylene glycol**) hexanoic acid 326892-09-5D, **conjugates** with human **insulin**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability and phys. characteristics of **orally** active amphiphilic human **insulin** analog, methoxy(**polyethylene glycol**) hexanoyl human recombinant **insulin**)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:722184 HCAPLUS
DOCUMENT NUMBER: 132:284007
TITLE: **Oral insulin** delivery: hydrolyzable amphiphilic **oligomer** **conjugates** prolong glucose reduction
AUTHOR(S): Ekwuribe, N.; Ramaswamy, M.; Allaudeen, H. S.; Rajagopalan, J. S.; Radhakrishnan, B.; Davis, C. M.; Regina, D. C.
CORPORATE SOURCE: Protein Delivery Inc., Durham, NC, 27713, USA
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1999), 26th, 147-148
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 Nov 1999
AB Insulin was chemical modified with hydrolyzable amphiphilic PEG derivative oligomers and they were formulated into microemulsions. Prolonged glucose reduction was observed following **oral** administration to dogs.
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2
ST **insulin conjugate PEG oligomer** **oral** delivery
IT Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fatty acyl esters and ethers, reaction products **insulin**, **oligomers**; hydrolyzable amphiphilic **oligomer**

conjugates prolong glucose reduction in **oral insulin** delivery)

IT Antidiabetic agents
(hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in **oral insulin** delivery)

IT Drug delivery systems
(**oral**; hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in **oral insulin** delivery)

IT **9004-10-8DP**, **Insulin**, reaction products with **PEG** derivative **oligomers**, biological studies **25322-68-3DP**, **Peg**, fatty acyl esters and ethers, reaction products **insulin**, **oligomers**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in **oral insulin** delivery)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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